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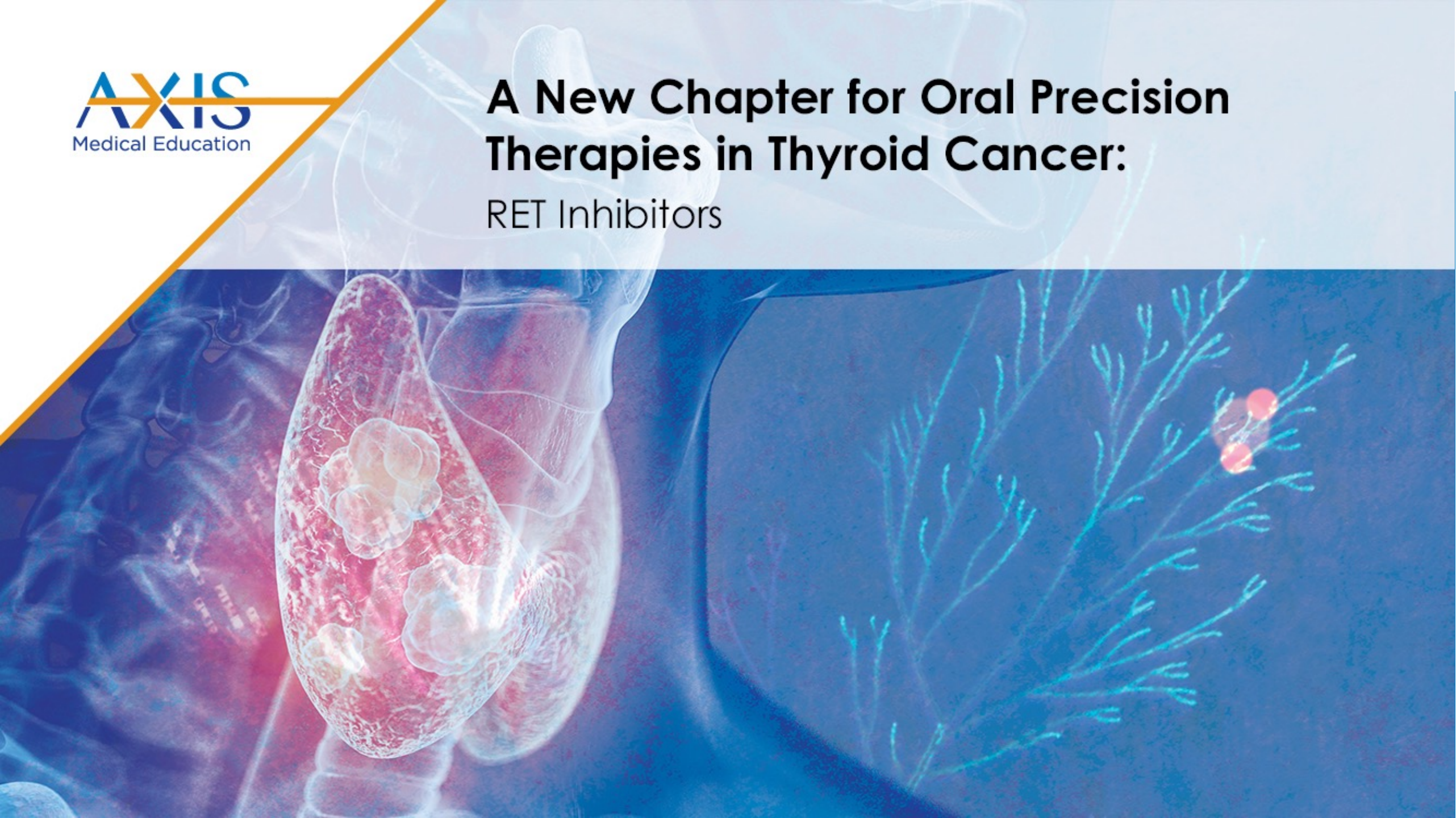
A New Chapter for Oral Precision Therapies in Thyroid Cancer:

RET Inhibitors



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Disclosure of Conflicts of Interest

Hyunseok "Hyu" Kang, MD, MPH, reported a financial interest/relationship or affiliation in the form of *Consultant*: Pin Therapeutics and Mito Immune. *Contracted research*: Lilly USA; Exelixis, Inc; Kura Oncology; PDS Biotechnology; Elevar Therapeutics; and NeoImmuneTech.

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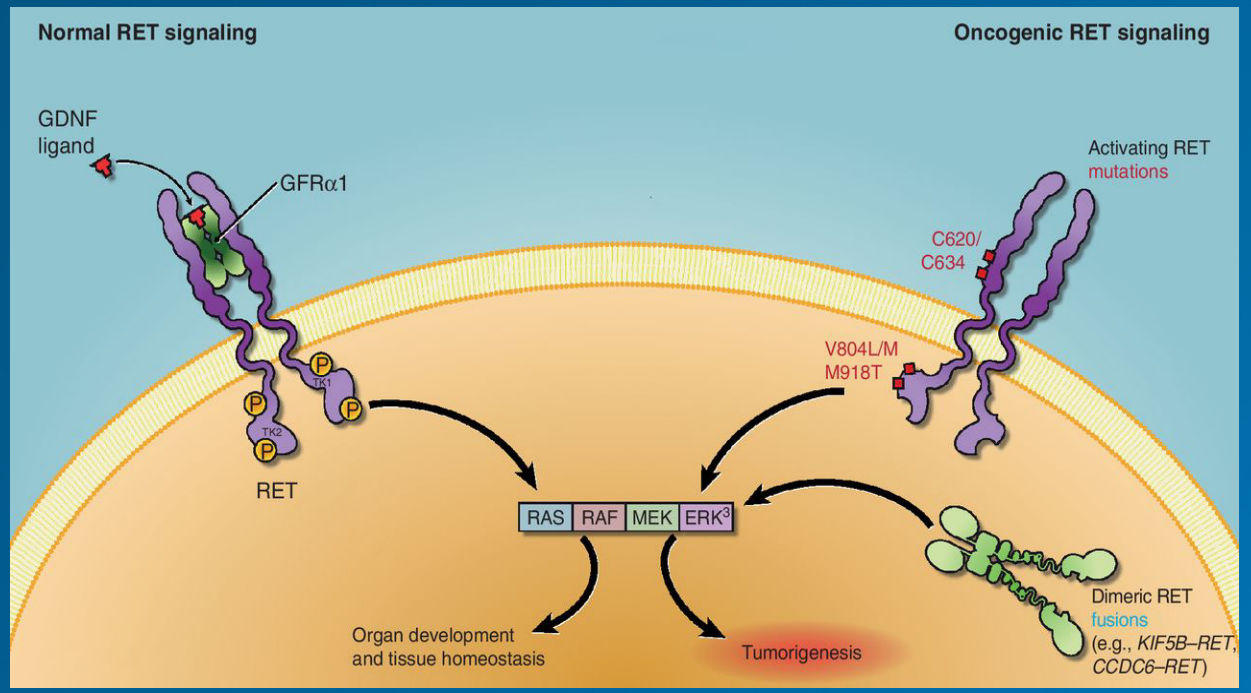
Learning Objectives

Upon completion of this activity, participants should be better able to:

- Describe the evolving evidence, rationale, and role of genomic testing in risk prognostication and the clinical impact of integrating this testing into practice for guiding therapy selection and optimal treatment decisions for thyroid cancer
- Analyze the outcomes data of RET-targeted therapy clinical trials, including patient morbidity and mortality, and the implications of these results on clinical practice to optimize treatment outcomes
- Develop treatment plans for patients with *RET*-fusion positive thyroid cancer based on the latest available clinical evidence, best practices, and guideline recommendations
- Apply the efficacy and safety of new and emerging RET-targeted treatment options for thyroid cancer patients with *RET* rearrangements into treatment strategies and to offer patients a better quality of life

Overview of *RET* Alterations in Thyroid Cancer

Proto-Oncogene *RE*arrangement During *T*ransfection (*RET*) and Its Significance



- RET is the receptor for glial cell-derived neurotrophic factor (GDNF) family of ligands
- It is a key molecule for organ development and tissue homeostasis
- Activating mutations and chromosomal rearrangements can cause constitutive activation of RET

Subbiah and Cote. *Cancer Discov* 2020;10(4):498-505.

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Medullary Thyroid Cancer

- A form of thyroid carcinoma arising from the parafollicular cells (C-cells) that produce calcitonin
- Accounts for <5% of thyroid cancer in the US with an estimated incidence of 0.21 cases per 100,000 population per year

Randle et al. *Surgery* 2017;161(1):137-146.

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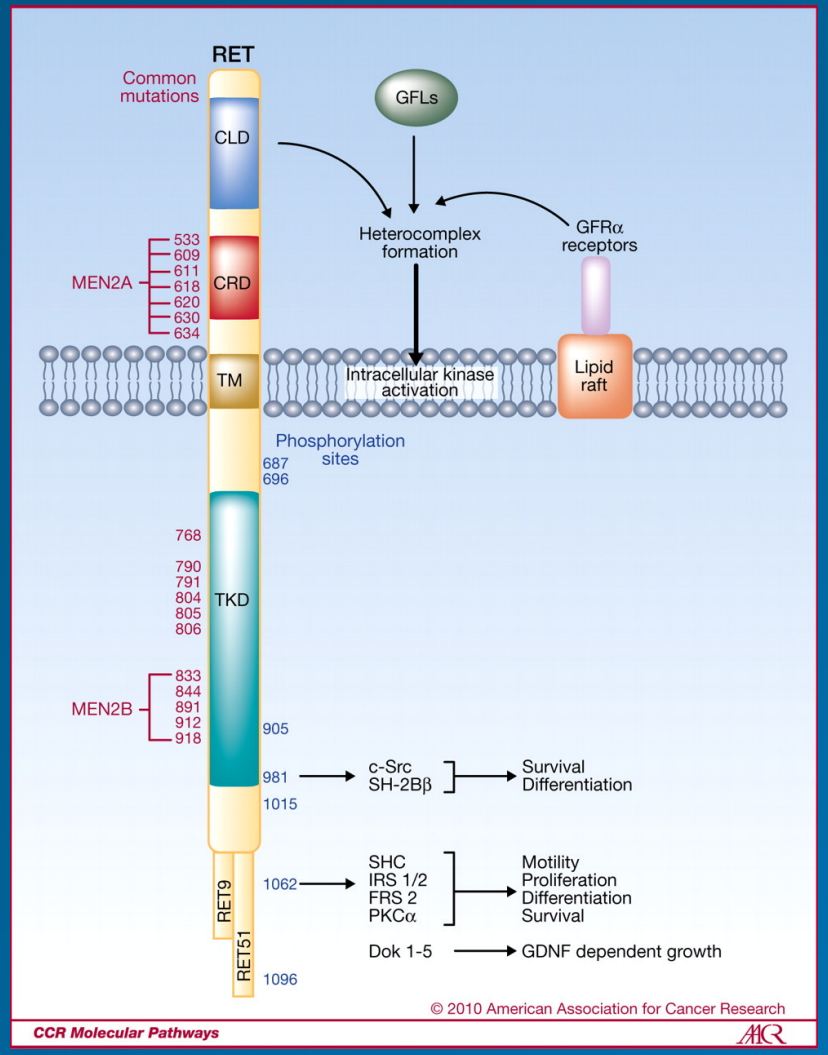
Activating *RET* Mutations in MTC



- 25% of MTC occurs as a hereditary monogenic autosomal dominant disorder in MEN2 syndrome (germline mutations)
- 55%-85% of patients with MTC have somatic *RET* mutations
  - M918T is the most prevalent, found in up to 40% of cases

MTC, medullary thyroid cancer.

Phay and Shah. *Clin Cancer Res.* 2010;16(24):5936-5941.
Salvatore et al. *Nat Rev Endocrinol.* 2021;17:296-306.

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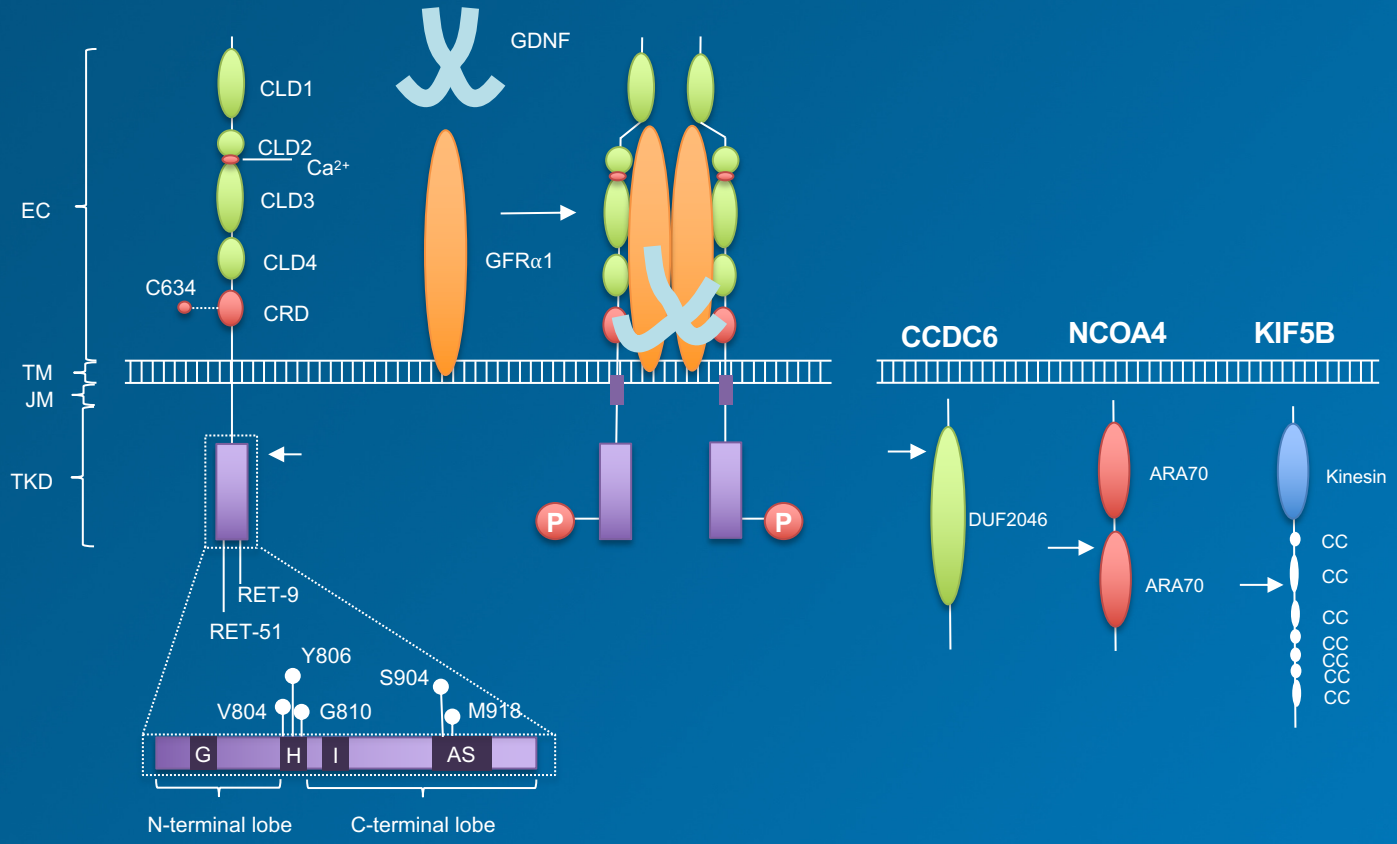
Activating *RET* Fusions in PTC and Other TCs



- *RET* kinase fusions occur in <10%-20% of patients with PTCs
- Most common in PTCs occurring after radiation exposure
- Can be present in poorly differentiated thyroid carcinoma and anaplastic thyroid carcinoma

PTC, papillary thyroid cancer; TC, thyroid cancer.
Adapted from Salvatore et al. *Nat Rev Endocrinol.* 2021;17:296-306.

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Historic Treatment Approaches & Need and Rationale for Newer Therapies

Surgery Options

- Total thyroidectomy +/- neck dissection is the preferred treatment option
- Surgical resection is preferred for locoregional recurrence, followed by radiation therapy

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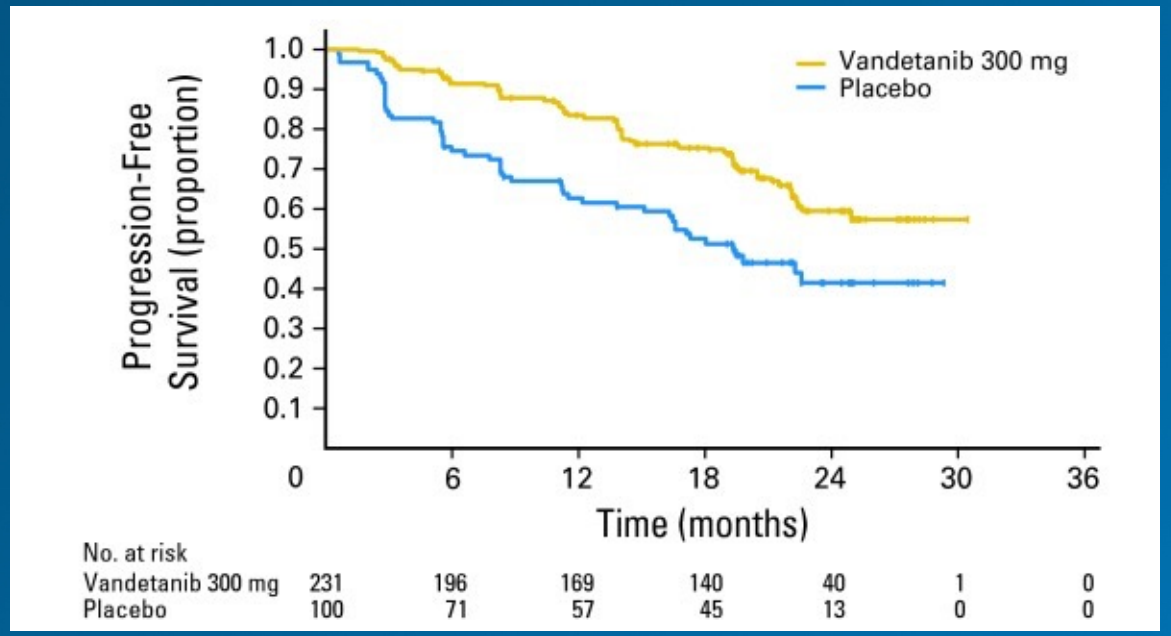
Multikinase Inhibitors for MTC

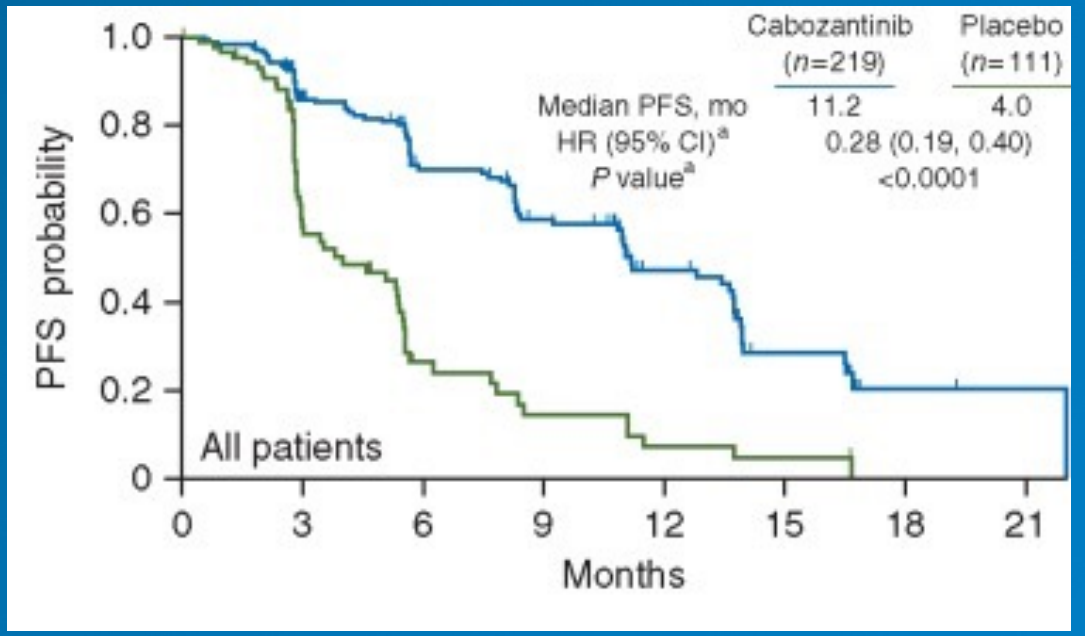
Vandetanib



Compared to placebo:

- ORR: 45% versus 13%
- mPFS: not reached (predicted 30.5 months by Weibull model) versus 19.3 months

Cabozantinib



Compared to placebo:

- ORR: 28% versus 0%
- mPFS: 11.2 months versus 4.0 months

mPFS, median progression-free survival; MTC, medullary thyroid cancer; ORR, overall response rate.
Wells et al. *J Clin Oncol* 2012;30:134-141. Schulmberger et al. *Ann Oncol* 2017;28:2813-2819.

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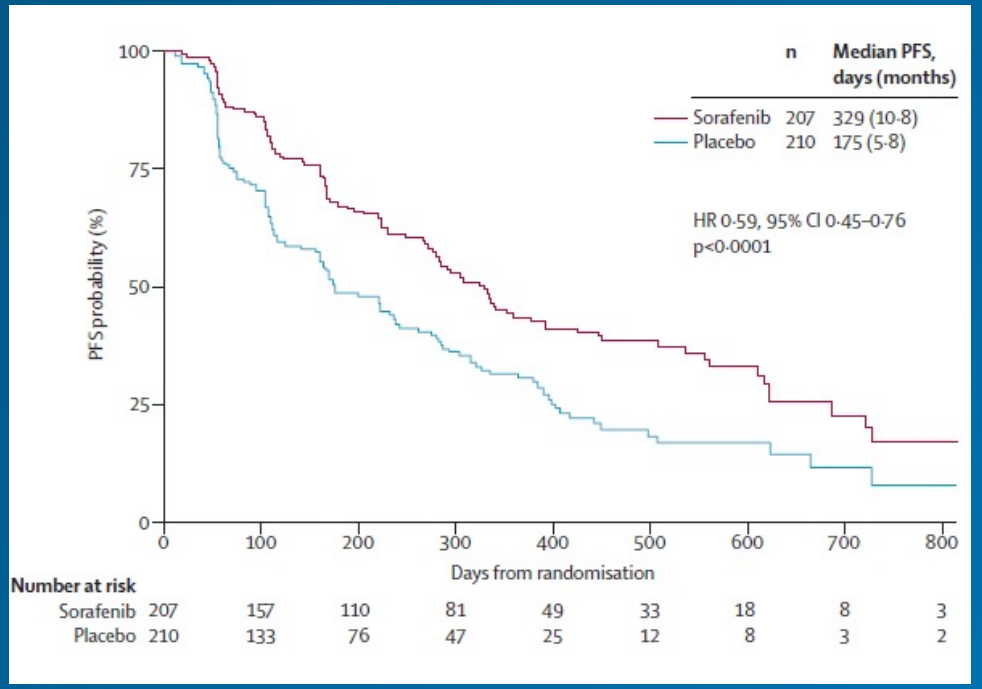
Multikinase Inhibitors for DTC

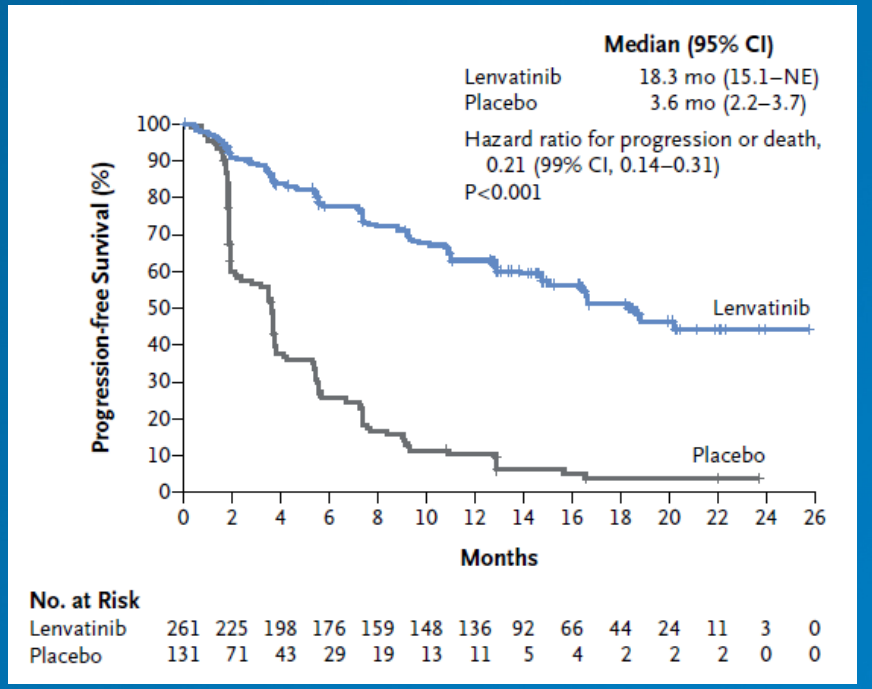
Sorafenib



Compared to placebo:

- ORR: 12.2% versus 0.5%
- mPFS: 10.8 months versus 5.8 months

Lenvatinib



Compared to placebo:

- ORR: 64.8% versus 1.5%
- mPFS: 18.3 months versus 3.6 months

DTC, differentiated thyroid cancer; mPFS, median progression-free survival; ORR, overall response rate.

Brose et al. *Lancet* 2014;384:319-328; Schlumberger et al. *N Engl J Med* 2015;372:621-630.

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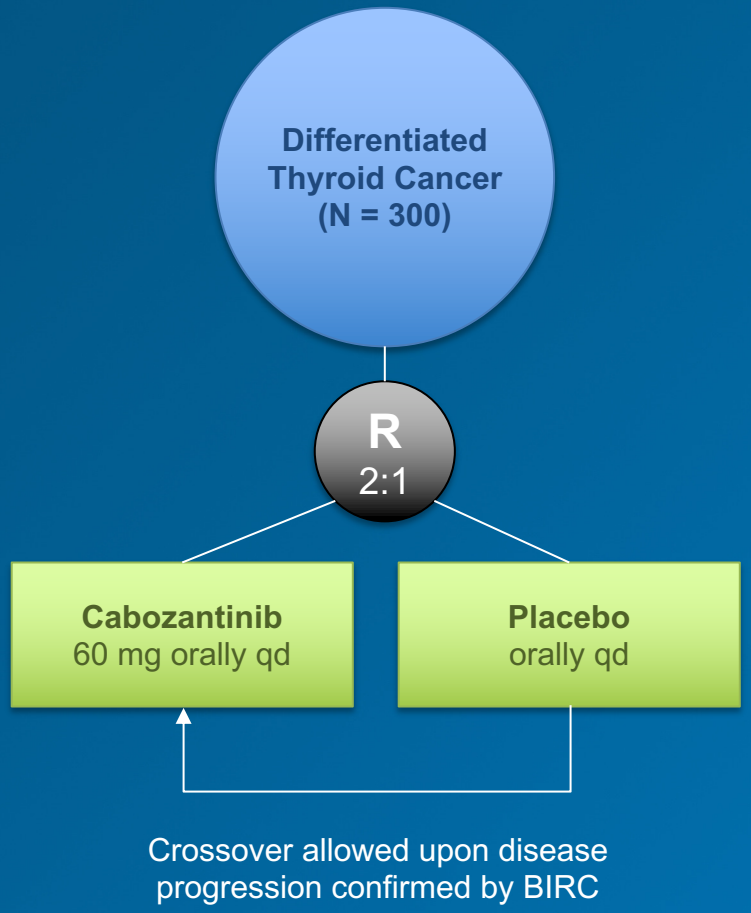
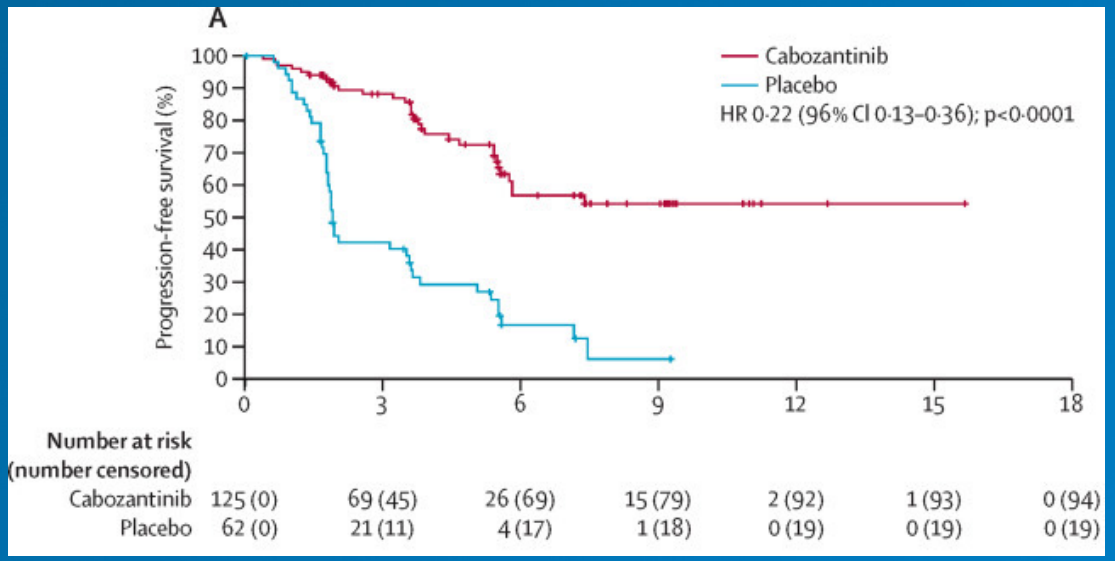
Multikinase Inhibitors for DTC: Cabozantinib (2nd Line) COSMIC-311





Compared to placebo:

- ORR: 15% versus 0%
- mPFS: not reached versus 1.9 months

BIRC, Blinded Independent Review Committee; DTC, differentiated thyroid cancer; mPFS, median progression-free survival; ORR, overall response rate.

Brose. *Lancet Oncol* 2021;22:1126-1138.

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Multikinase Inhibitors in MTC and DTC

- Vandetanib and cabozantinib demonstrated significant PFS benefits in MTC patients
- Sorafenib, lenvatinib and cabozantinib demonstrated significant PFS benefits in DTC patients
- However, these agents cause significant treatment related adverse events which limits their tolerability for patients
  - Hypertension, proteinuria, decreased appetite, electrolyte abnormalities, hand-foot syndrome, bleeding events, etc.
- Discontinuation rates:
  - Vandetanib: 12%
  - Cabozantinib: 16%
  - Sorafenib: 19%
  - Lenvatinib: 14%

DTC, differentiated thyroid cancer; MTC, medullary thyroid cancer; PFS, progression-free survival.

Wells et al. *J Clin Oncol* 2012;30:134-141; Elisei et al. *J Clin Oncol* 2013;31:3639-3646; Brose et al. *Lancet* 2014;364:319-328; Schlumberger et al. *N Engl J Med* 2015;372:621-630.

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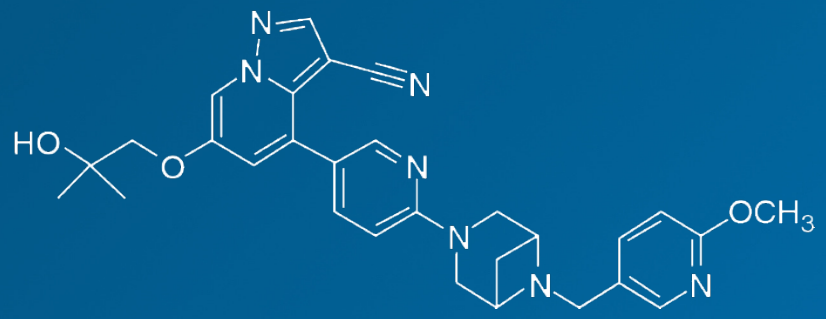
Approved and Investigational Agents for *RET*-altered or *RET*-driven Thyroid Cancer

Selpercatinib



- A highly selective RET inhibitor
- Oral administration based on weight:
  - Less than 50 kg: 120 mg orally twice daily
  - 50 kg or greater: 160 mg orally twice daily
- Approved for metastatic *RET* fusion–positive NSCLC, advanced or metastatic *RET*-mutant MTC, and advanced or metastatic RAI-refractory *RET* fusion-positive thyroid cancer

MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; RAI, radioactive iodine.
Wirth et al. *N Engl J Med* 2020; 383:825-835.

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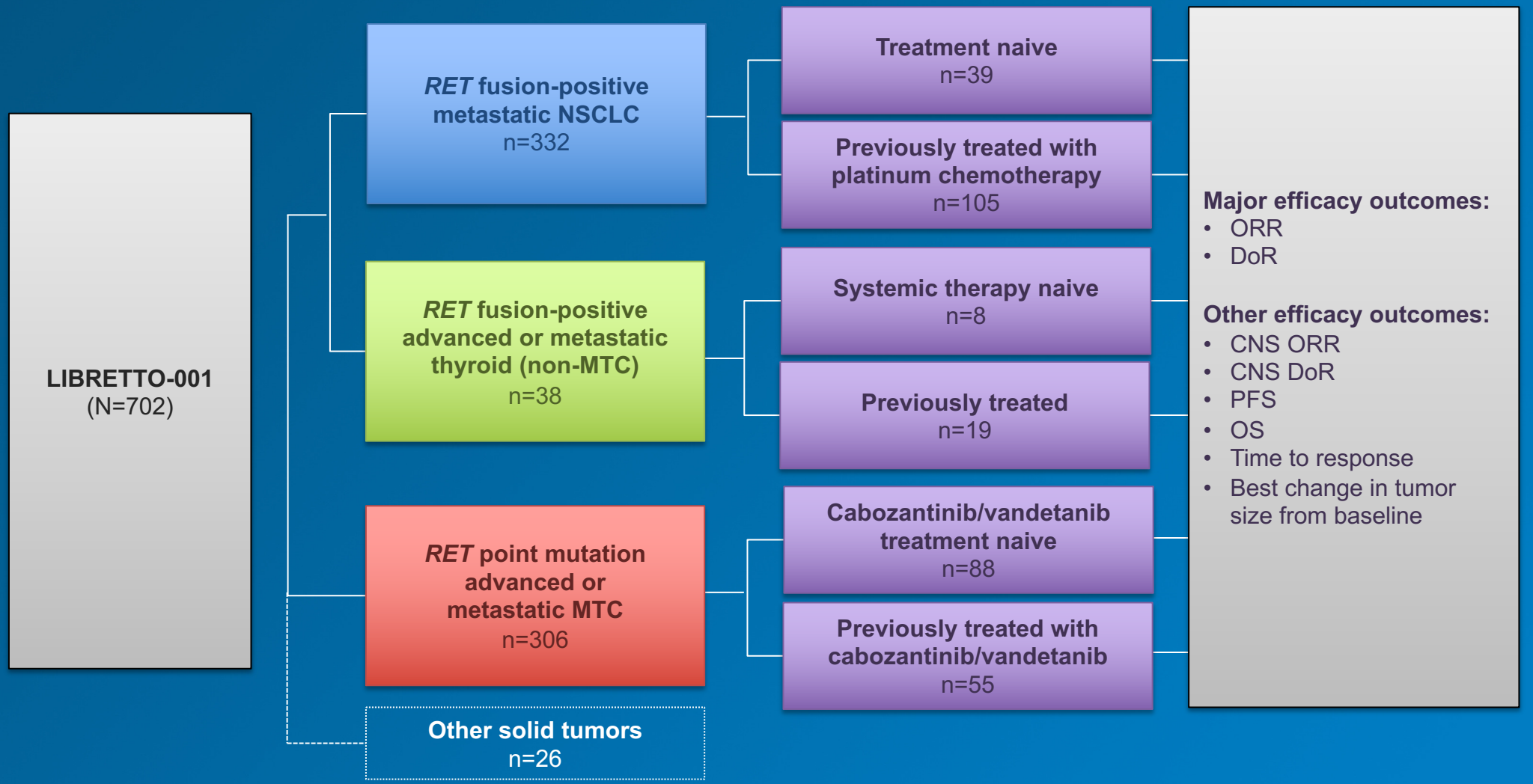
LIBRETTO-001: Trial Design



CNS, central nervous system; DoR, duration of response; MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Wirth et al. *N Engl J Med.* 2020;383:825-835.

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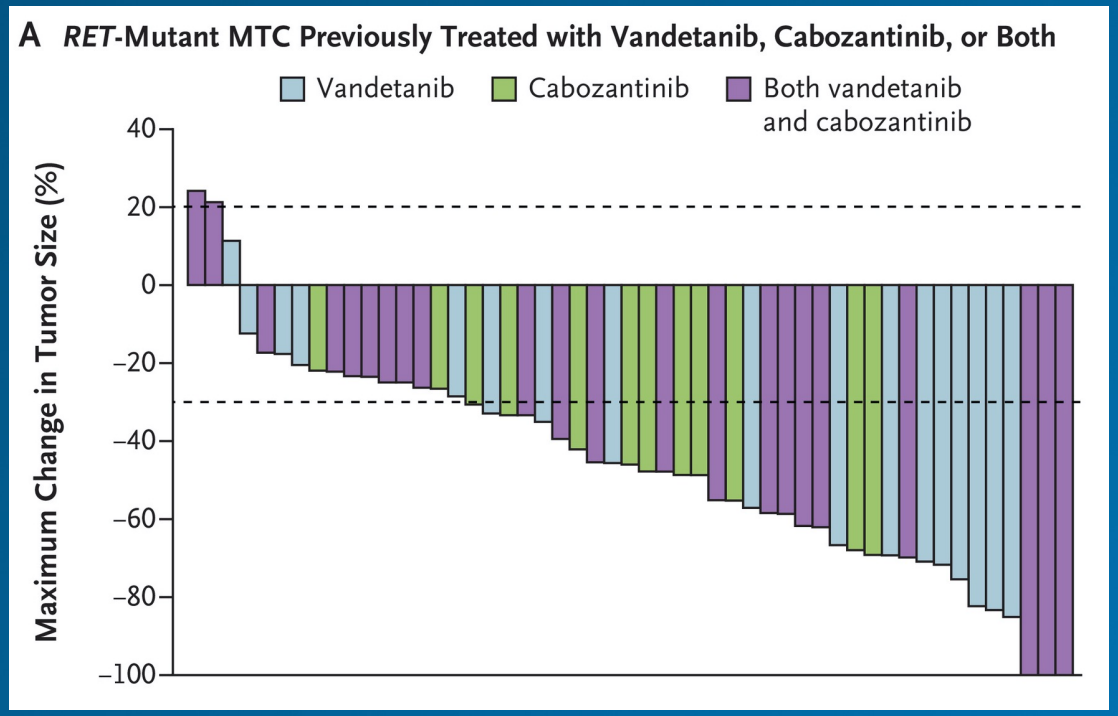
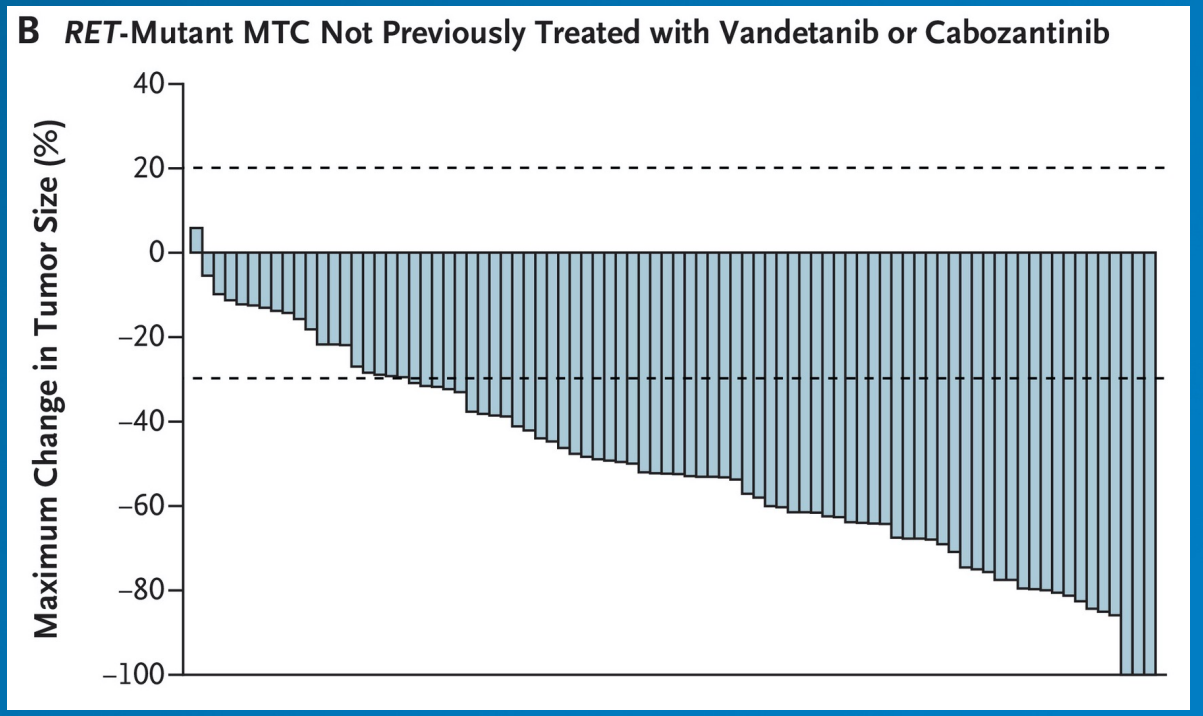
LIBRETTO-001: Efficacy Results

RET mutation–positive MTC



ORR 69% (in TKI pre-treated MTC, n = 55)



ORR 73% (in TKI naïve MTC, n = 88)

MTC, medullary thyroid cancer; ORR, objective response rate; TKI, tyrosine kinase inhibitor.

Wirth et al. *N Engl J Med* 2020;383:825-835.

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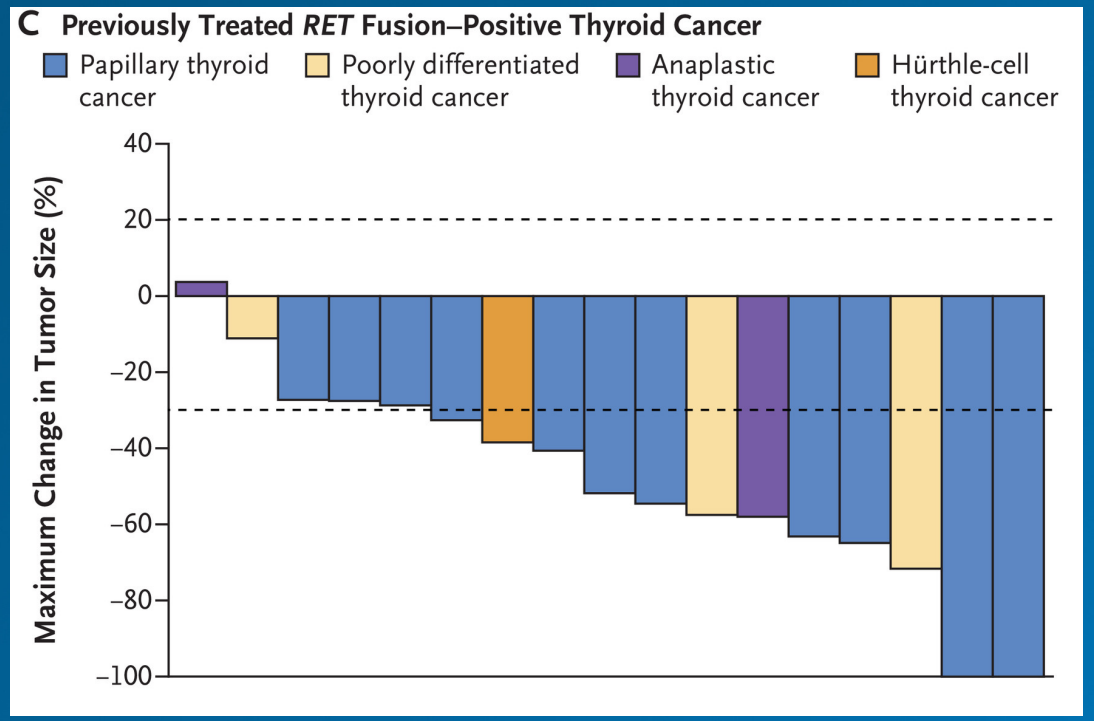
LIBRETTO-001: Efficacy Results

RET fusion–positive thyroid cancers



- ORR 71% (n = 19)
- Responders include 1 patient with anaplastic thyroid cancer and 2 patients with poorly-differentiated thyroid cancer

MTC, medullary thyroid cancer; ORR, overall response rate; TKI, tyrosine kinase inhibitor.
Wirth et al. *N Engl J Med* 2020;383:825-835.

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LIBRETTO-001: Updated Analysis

RET-altered thyroid cancer

	Primary Analysis Set (the first 55 enrolled patients; n = 55)	Integrated Analysis Set (TKI-pretreated MTC; n = 143)	Cabozantinib/ Vandetanib-naïve MTC (n = 112)	RET-Fusion TC (with prior systemic treatment; n = 22)
ORR, %	69.1	69.2	71.4	77.3
CBR, %	92.7	90.9	93.8	100.0
DoR, median, months	NE	NE	21.95	18.4
Duration of follow-up, months	17.45	10.05	9.26	20.27
Rate (%) PFS, > 12 months	82.3	76.9	92.9	68.6

Phase 3 trial (LIBRETTO-531) evaluating selpercatinib compared to cabozantinib/vandetanib in kinase inhibitor-naïve MTC patients is ongoing

CBR, clinical benefit rate; DoR, duration of response; NE, not estimated; ORR, overall response rate; PFS, progression-free survival; TC, thyroid cancer.
Integrated analysis set (IAS, n = 143) includes efficacy evaluable MTC pts previously treated with cabozantinib and/or vandetanib.
The primary analysis set (PAS), a subset of IAS, is the first 55 enrolled pts. Cabo/vande naïve MTC pts (N = 112) and TC pts with prior systemic treatment (N = 22) were also analyzed.
Sherman et al. *J Clin Oncol*. 2021;39(15):6073.

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LIBRETTO-001: Safety and Adverse Events

RET-altered thyroid cancer

Treatment-related AEs

Number of patients (%)	Grade 3	Grade 4
Any AE	45 (28)	3 (2)
Hypertension	19 (12)	0
Diarrhea	4 (3)	0
Fatigue	1 (1)	0
Elevated AST	12 (7)	1 (1)
Elevated ALT	16 (10)	1 (1)
Headache	1 (1)	0
QT prolongation	3 (2)	0
Weight gain	1 (1)	0

- Generally well tolerated with few grade 4 AEs
- Common AEs:
  - Dry mouth, hypertension, elevated AST/ALT
- Discontinuation rate for toxicity:
  - 2% (12 of 531)

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Wirth et al. *N Engl J Med* 2020;383:825-835.

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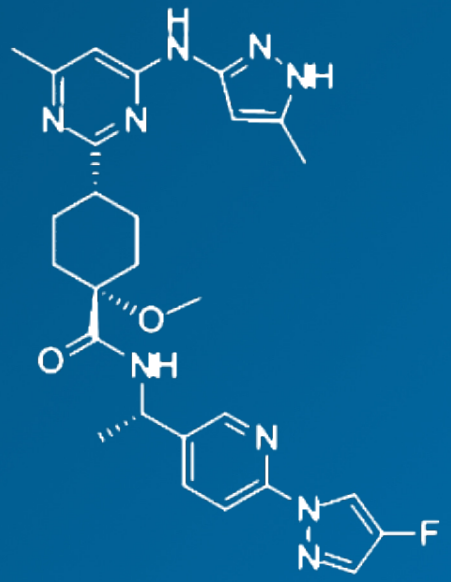
Pralsetinib



- A highly selective RET inhibitor
- Oral administration at 400 mg once daily
- Approved for metastatic *RET* fusion–positive NSCLC, advanced or metastatic *RET*-mutant MTC, and advanced or metastatic RAI-refractory *RET* fusion-positive thyroid cancers

MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; RAI, radioactive iodine.

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ARROW: Trial Design

Phase 2

- Advanced solid tumors
- RET-altered (local testing)
- No other driver mutations
- ECOG PS 0-1

Pralsetinib dosing:
400 mg PO QD

- ***RET* fusion-positive NSCLC**
- ***RET* mutation-positive MTC**
- ***RET* fusion-positive other tumors**

Primary endpoints

- Centrally reviewed ORR per RECIST v1.1
- Safety

ECOG, Eastern Cooperative Oncology Group; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors.
Subbiah et al. *Lancet Diabetes Endocrinol* 2021;9:491-501.

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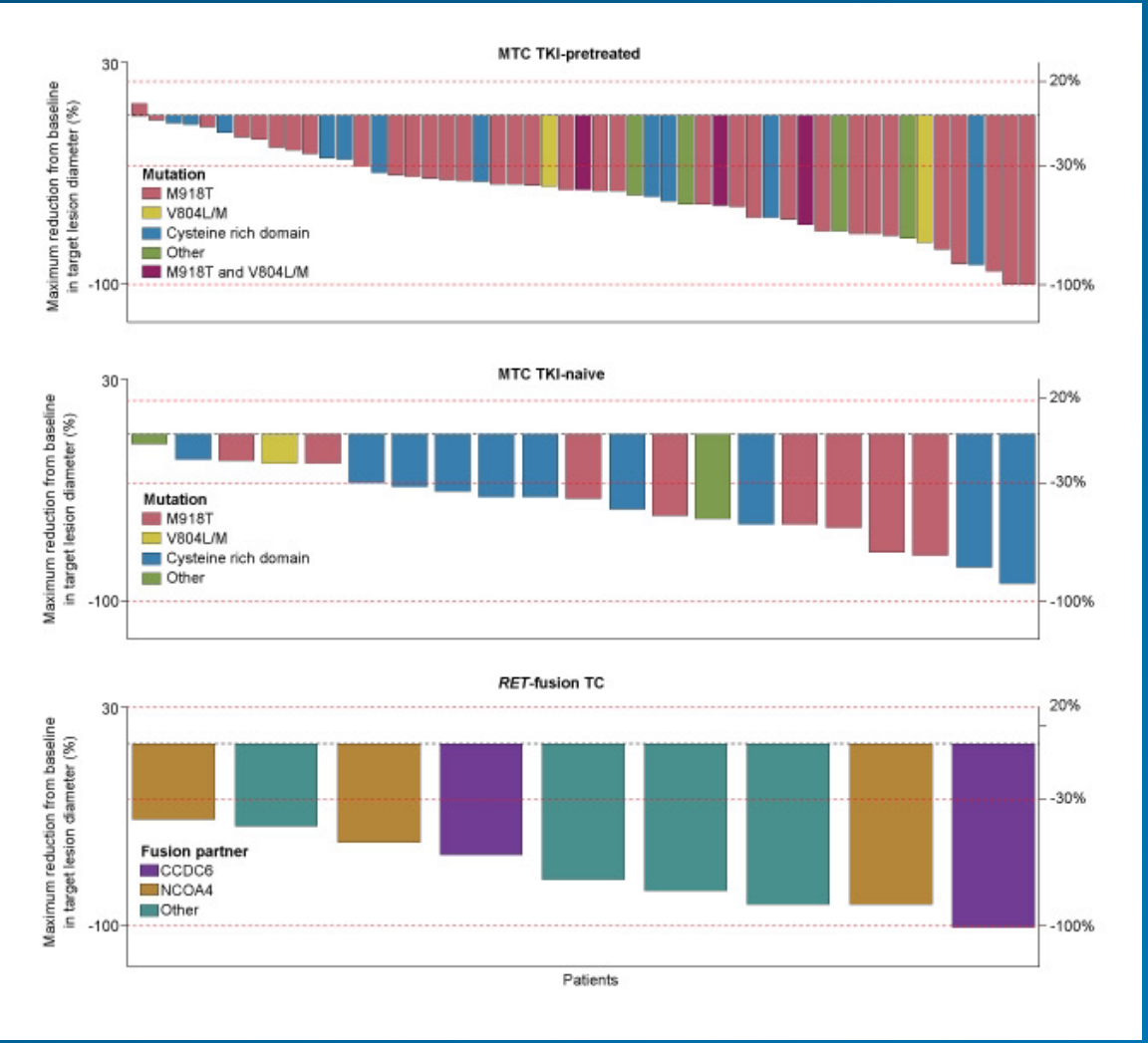
ARROW: Efficacy Results



ORR:

- 60% in TKI-pretreated MTC (n = 55)
- 71% in TKI-naïve MTC (n = 21)
- 89% in *RET*-fusion positive TC (n = 9; all patients had RAI-refractory DTC)

DTC, differentiated thyroid cancer; MTC, medullary thyroid cancer; ORR, overall response rate; RAI, radioactive iodine; TKI, tyrosine kinase inhibitor.
Adapted from Subbiah et al. *Lancet Diabetes Endocrinol* 2021;9:491-501.

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ARROW: Safety and Adverse Events

Treatment-related AEs

Number of patients (%)	Grade 3	Grade 4/5
Any AE	67 (47)	9 (7)
Hypertension	24 (17)	0
Neutropenia	18 (13)	1 (1)
Anemia	14 (10)	0
Lymphopenia	15 (11)	2 (1)
Asthenia	6 (4)	0
Pneumonitis	4 (3)	0
Diarrhea	3 (2)	0
Thrombocytopenia	2 (1)	2 (1)
Pneumonia	0	1 (grade 5)

- Generally well tolerated with few grade 4 AEs
- Common AEs:
  - Elevated AST/ALT, decreased WBC, neutropenia, hypertension
- Discontinuation rate for toxicity:
  - 4% (5 of 142)

AEs, adverse events; AST, aspartate aminotransferase.
Subbiah et al. *Lancet Diabetes Endocrinol* 2021;9:491-501.

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Highlights
Selpercatinib and Pralsetinib

	Selpercatinib	Pralsetinib
Administration, dose	Oral, 160 mg ***twice daily*** (less than 50 kg: 120 mg)	Oral, 400 mg ***once daily***
ORR		
TKI-naïve MTC	73% (n = 88)	60% (n = 55)
TKI pre-treated MTC	69% (n = 55)	71% (n = 21)
***RET* fusion-positive TC**	71% (n = 19)	89% (n = 9)
Adverse events		
Any Grade 3-5 Treatment-related AE	30%	53%

AE, adverse event; MTC, medullary thyroid cancer; ORR, overall response rate; TKI, tyrosine kinase inhibitor.

Subbiah et al. *Lancet Diabetes Endocrinol* 2021;9:491-501; Wirth et al. *N Engl J Med* 2020;383:825-835.

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Investigational Agents: TPX-0046

- TPX-0046 is a multi-targeted RET and SRC kinase inhibitor that demonstrated inhibition of RET with solvent-front mutations
- In a phase 1 study, 3 of 9 pretreated patients with NSCLC and MTC showed tumor regression (1 PR)
- Phase 2 study for NSCLC, MTC, and *RET*-altered solid tumors are ongoing (NCT04161391)

MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; PR, partial response.

Caner Network. April 6, 2021. https://www.cancernetwork.com/view/investigational-ret-inhibitor-tpx-0046-show-preliminary-clinical-activity-in-nsclc-mtc

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Investigational Agents: BOS172738

- BOS172738 is a highly selective oral RET and VEGFR2 inhibitor with demonstrated activity against gatekeeper mutations
- In a phase 1 study, ORR for *RET*-altered cancers (including NSCLC and MTC) was 31% (n=54), ORR in MTC was 44% (n=16)
- Phase 1 dose expansion study for NSCLC and MTC is ongoing (NCT03780517)

MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; ORR, objective response rate; VEGFR2, vascular endothelial growth factor receptor 2.
Schoffski et al. *J Clin Oncol*. 2021;39(15):3008.

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Investigational Agents: TAS0953/HM06

- TAS0953/HM06 is a second-generation RET inhibitor with activity against known *RET* resistance mutations (solvent-front mutations)
- A phase 1/2 study for *RET*-altered NSCLC and solid tumors is ongoing (NCT04683250)
  - Preliminary results demonstrate potency against the *RET* solvent-front mutation resistance mechanism

NSCLC, non-small cell lung cancer.
Helsinn Healthcare SA. October 7, 2021. https://finance.yahoo.com/news/helsinn-group-announces-oral-presentation-130000107.html

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Investigational Agents: Others

- LOX-18228 and LOX-19260 are potent and selective next-generation RET inhibitors for *RET* V804 gatekeeper and G810 solvent-front mutations
- They are in preclinical development and an investigational new drug application is planned

Thein et al. *Trends in Cancer* 2021;7(12):1074-1088.

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Summary and Future Directions

- Highly selective RET inhibitors, selpercatinib and pralsetinib, demonstrated impressive activities and safety profiles, and are FDA approved for advanced and metastatic *RET* mutation–positive MTC and *RET* fusion–positive TCs
- Second-generation RET inhibitors for emerging resistance mutations (solvent-front and gatekeeper mutations) are under development

FDA, US Food & Drug Administration; MTC, medullary thyroid cancer; TC, thyroid cancer.

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Importance of Molecular Diagnostic Testing

How to Detect *RET* Alterations

RET point mutations: germline and somatic

- Quantitative PCR
  - Well-established test to detect point mutations
  - Limited to a single gene and potentially a limited coverage of the gene
- Sanger sequencing
  - Low sensitivity and limited coverage of the gene
- Next-generation sequencing

RET fusions: somatic

- Fluorescence in situ hybridization
  - Detects fusions regardless of fusion partner
  - Can have false-negative results if the probe binds to area close to a partner gene
- Reverse transcription PCR
  - Fast turnaround and sensitive, but does not detect unknown fusion partner
- Next-generation sequencing

PCR, polymerase chain reaction.

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Testing for *RET* alteration in MTC

- NCCN recommends germline *RET* mutation testing for all newly-diagnosed MTC
  - 6% of patients with clinically sporadic MTC carry a germline mutation in *RET*
- NCCN states that *RET* somatic genotyping may be done in patients who are germline wild-type or if germline status is unknown

MTC, medullary thyroid cancer.

NCCN Clinical Practice Guidelines in Oncology. Thyroid Cancer. Version 3.2021. https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf

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Molecular Profiling for DTC

- NCCN Guidelines recommend genomic testing to identify potentially actionable mutations (eg, *ALK*, *NTRK*, and *RET* gene fusions; DNA mismatch repair deficiency, microsatellite instability, tumor mutational burden) for metastatic DTC

- ATA 2021 guidelines recommend genomic testing for ATC

ATA, American Thyroid Association; ATC, anaplastic thyroid cancer; DTC, differentiated thyroid cancer; NCCN, National Comprehensive Cancer Network.

NCCN Clinical Practice Guidelines in Oncology. Thyroid Cancer. Version 3.2021.. https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf;
Bible et al. *Thyroid;*2021:337-386.

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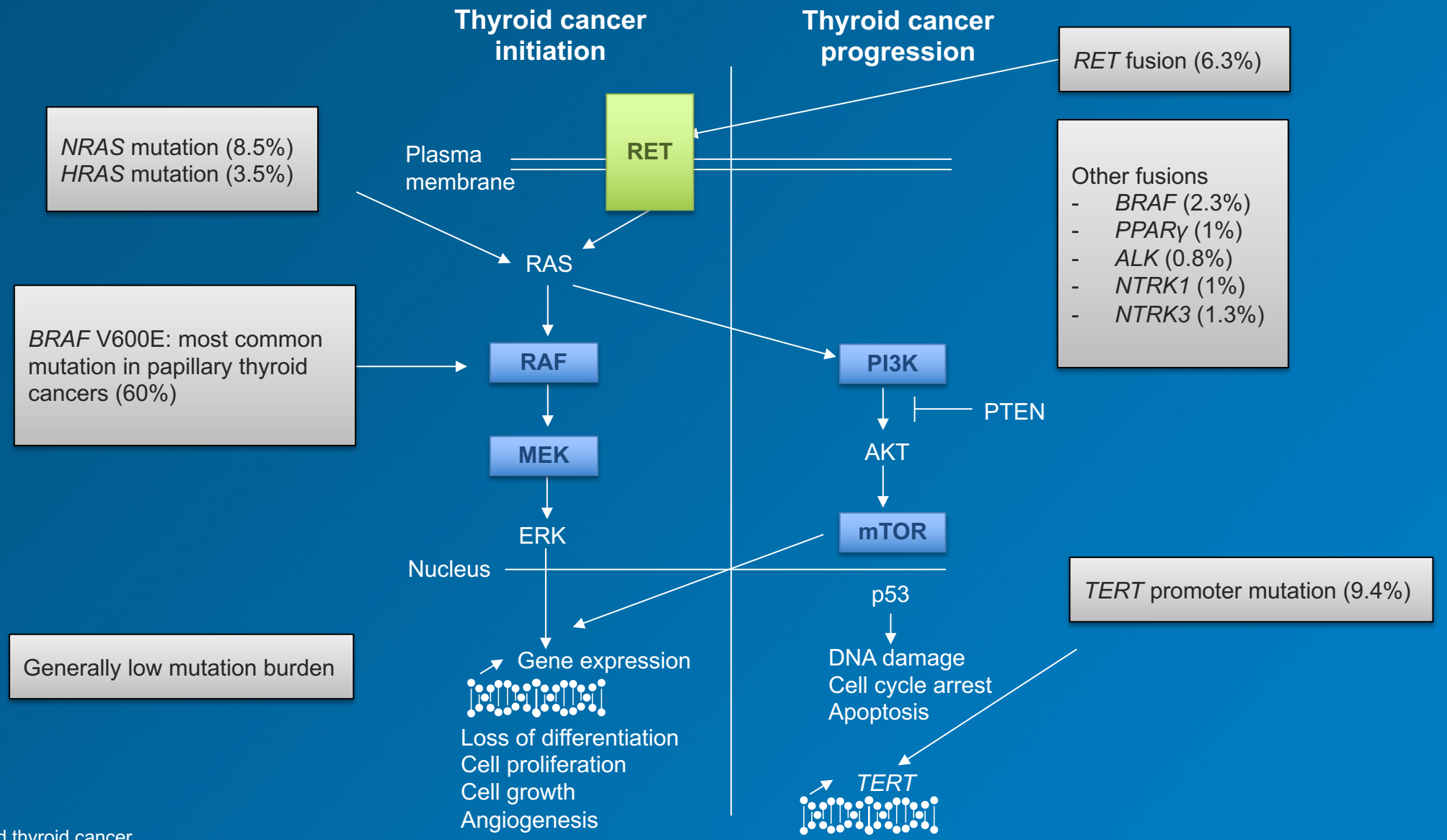
Biology of DTC



DTC, differentiated thyroid cancer.
Adapted from Cabanillas et al. *Lancet* 2016;388:2783-2795.

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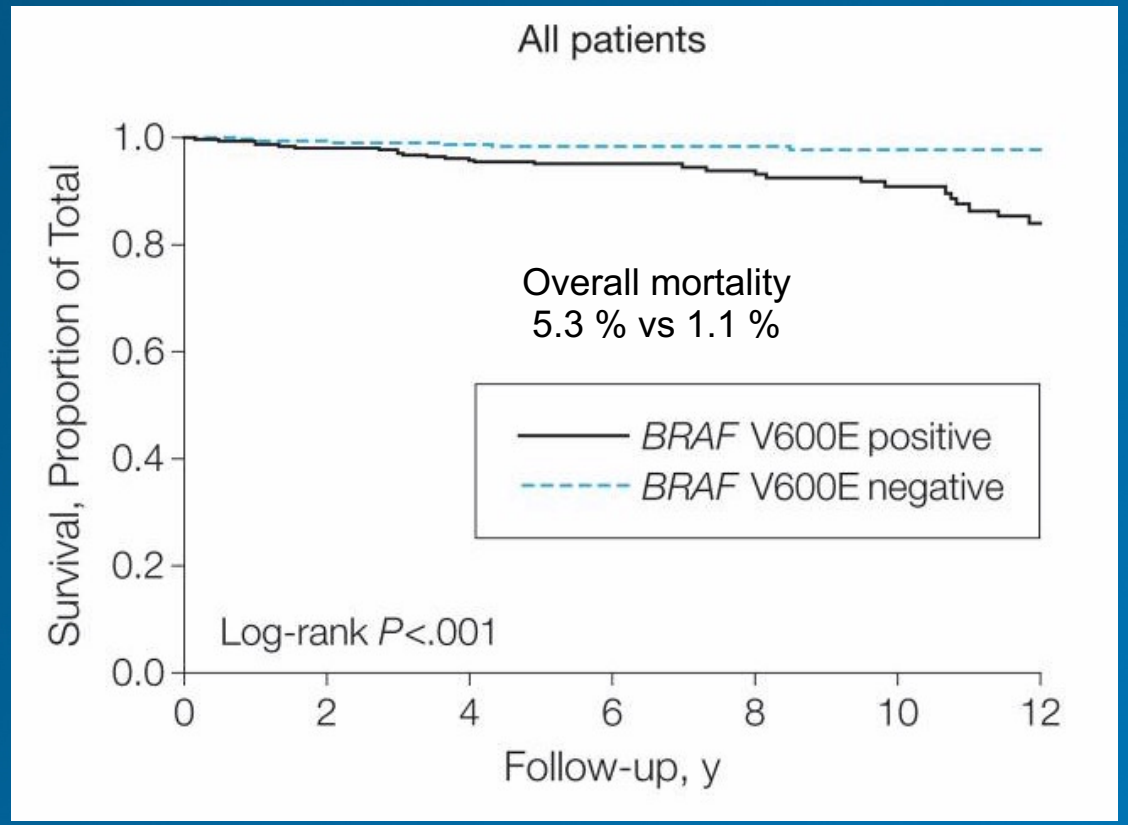
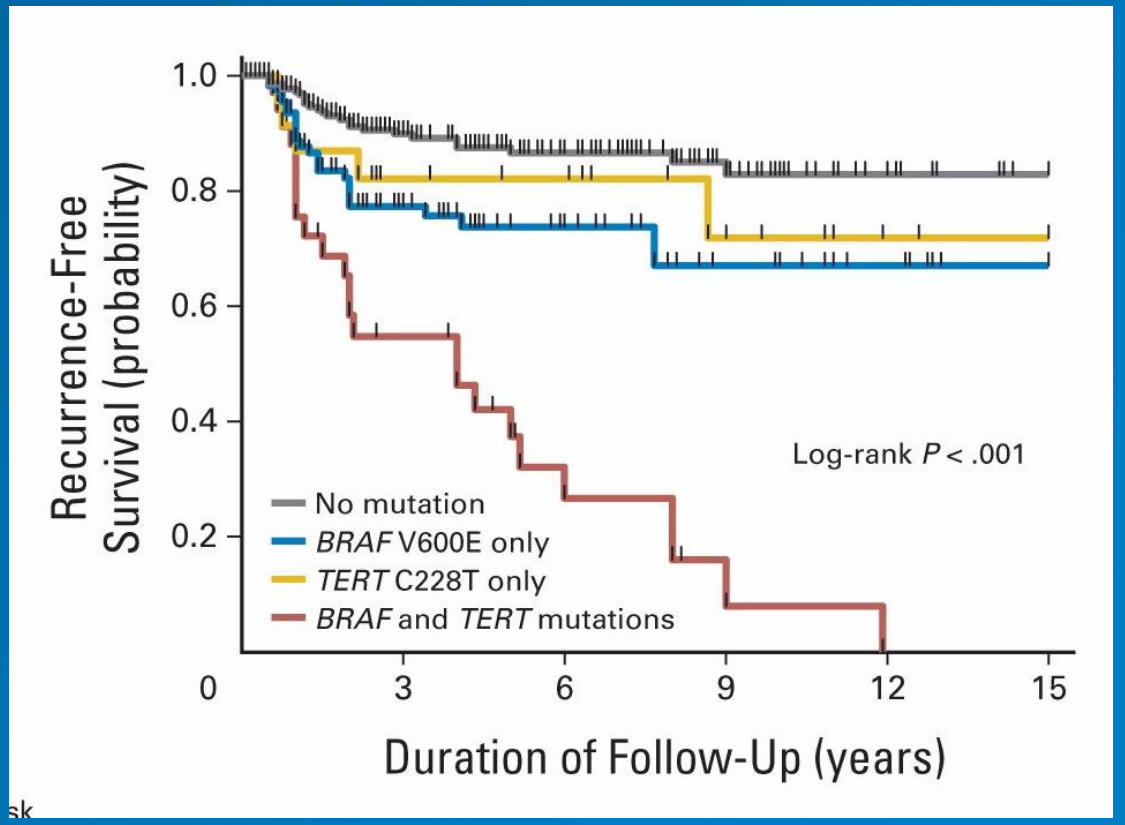
Comprehensive Genomic Profiling May Provide Prognostic Information for DTC

BRAF mutation-positive DTC has poorer prognosis



BRAF + *TERT* mutation-positive PTC has poorer prognosis



DTC, differentiated thyroid cancer; PTC, papillary thyroid cancer.

Xing et al. *JAMA* 2013;10;309:1493-1501; *J Clin Oncol* 2014;32:2718-2726.

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Comprehensive Genomic Profiling

Testing Scopes

- Targeted DNA sequencing: sequences selected cancer-related genes using DNA only
- Targeted DNA and RNA sequencing: sequences selected cancer-related genes using DNA and RNA, which is more sensitive for fusion detection, including unknown fusion partner
- Whole exome sequencing: sequences the entire protein-coding region

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Comprehensive Genomic Profiling

Specimen Types

- Tumor profiling: uses tumor specimen (biopsy or surgical specimen)
- Liquid biopsy: uses circulating tumor DNA (ctDNA)
- Germline sequencing: uses normal cells (blood cells)

Mutation Calling

- Tumor-only sequencing: calls variants based on bioinformatics pipeline
- Matched normal/tumor sequencing: calls variants based on difference between normal genes and tumor genes

AXIS Medical Education

Considerations for Choosing an Assay

Germline versus Tumor Test

- MTC patients need germline testing and potentially genetic counseling
- MTC patients without germline mutation and other TC patients need tumor genomic profiling

NGS versus PCR/FISH

- Consider turnaround time
- Generally, NGS is preferred, given the depth of information available

FISH, fluorescence in situ hybridization; MTC, medullary thyroid cancer; NGS, next-generation sequencing; PCR, polymerase chain reaction; TC, thyroid cancer.

AXIS Medical Education

Considerations for Choosing an Assay

Targeted Cancer Gene Sequencing vs. Whole Exome Sequencing (WES)

- WES is more expensive
- WES may not achieve sequencing depth (number of times a given nucleotide is sequenced) as well as targeted sequencing and can be less accurate in detecting low-frequency alterations

RNA Sequencing

- A panel including RNA sequencing may be more accurate in detecting fusion genes and fusions with an unknown partner

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Long-Term Oral Therapy Compliance Considerations

Once a Day vs Twice a Day
Is There a Concern?

- Adherence to oral cancer therapy has been a problem
- A systematic literature review suggests that the rate of adherence to oral cancer drugs is as low as 46%
- Factors associated with nonadherence include:
  - Complex treatment regimen
  - Substantial behavior change required
  - Inadequate supervision
  - Poor communication

Greer et al. *Oncologist* 2016;21:354-376.
Thomas et al. *US Pharm* 2019;44:HS9-HS12.

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Once a Day vs Twice a Day
Is There a Concern?

- Both selpercatinib and pralsetinib have relatively simple, consistent dosing schedules
  - Selpercatinib: comes in 40 mg and 80 mg capsules
    - <50 kg: 120 mg orally twice daily
    - ≥50 kg: 160 mg orally twice daily
  - Pralsetinib: comes in 100 mg capsules
    - 400 mg orally once daily on an empty stomach
- Both have very favorable safety profiles

Greer et al. *Oncologist* 2016;21:354-376; Thomas et al. *US Pharm* 2019;44:HS9-HS12; selpercatinib prescribing information, 2021; pralsetinib prescribing information, 2020.

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Other Differences in Administration

- Selpercatinib:
  - May be taken with or without food
  - Acid-reducing agents: Avoid coadministration. If coadministration cannot be avoided, take selpercatinib with food (with PPI) or modify its administration time (with H2 receptor antagonist or locally-acting antacid)

- Pralsetinib:
  - Must be taken on an empty stomach; no food intake for 2+ hours before and 1+ hour after each dose
  - PPIs and H2 receptor antagonists do not need to be avoided

PPI, proton pump inhibitor.
Selpercatinib prescribing information, 2021; pralsetinib prescribing information, 2020.

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Resistance Challenges

Resistance Mechanisms

- Resistance to RET inhibitors was studied mainly in *RET* fusion–positive NSCLC
  - Acquired alterations in other genes (MET or KRAS amplification)
  - Acquired mutation in RET G810 (solvent-front mutation)
  - Selpercatinib and pralsetinib are active against *RET* gatekeeper mutations

NSCLC, non-small cell lung cancer.
Lin et al. *Ann Oncol* 2020;31:1725-1733.

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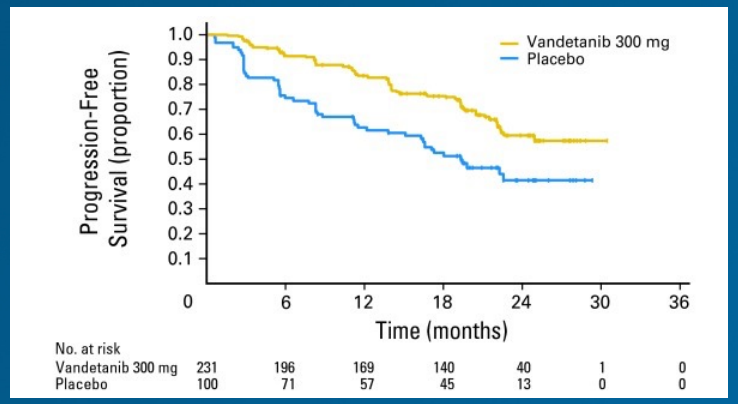
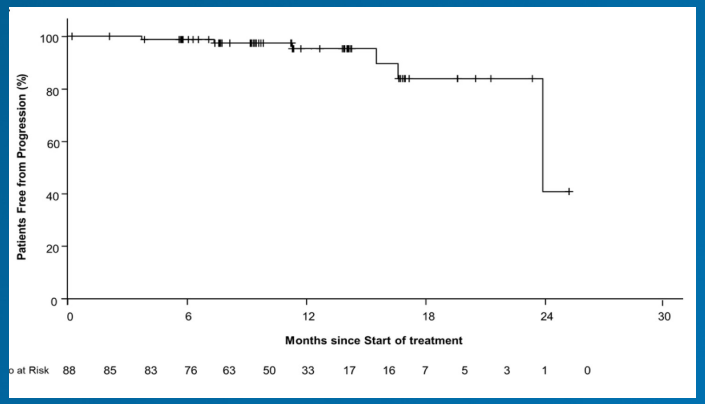
MKI vs Selective RET Inhibitor in Treatment-Naïve MTC Patients: PFS

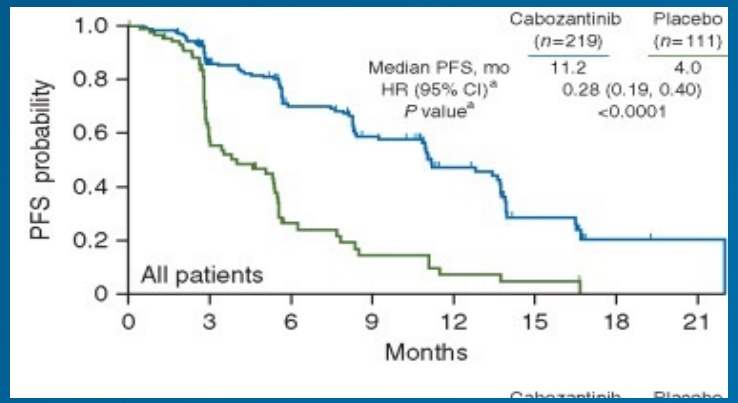
Vandetanib



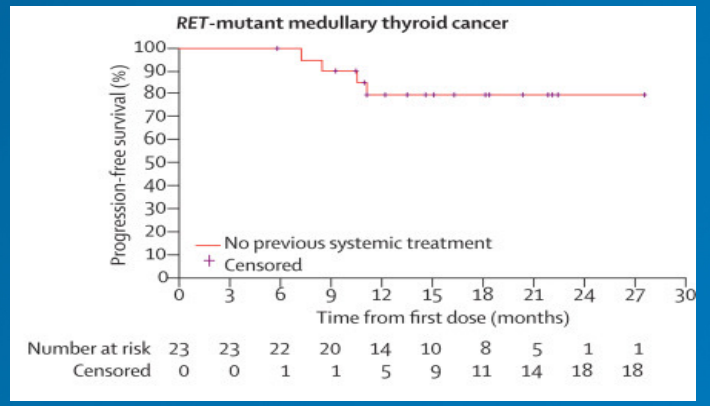
Selpercatinib



Cabozantinib



Pralsetinib



- PFS curves do not suggest more resistance development in patients treated with highly selective RET inhibitor, compared to MKIs

MKI, multikinase inhibitor; MTC, medullary thyroid cancer; PFS, progression-free survival.

Wells et al. *J Clin Oncol*. 2012;30:134-141; Elisei et al. *J Clin Oncol*. 2013;31:3639-3646;
Wirth et al. *N Engl J Med*. 2020;383(9):825–835; Subbiah et al. *Lancet Diabetes Endocrinol*. 2021;9(8):491-501.

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Is Dual or Combination Therapy More Effective?

- Possibly
- However, dual or combination therapy will certainly increase toxicity and may impact treatment tolerability
- Alternative oncogene amplification may allow for resistance to dual/combination therapy (tumor can develop alterations in a bypass pathway)

AXIS Medical Education

Virtual Case Clinic

Case: Patient Presentation and Medical History

Presentation

- 42-year-old female, never smoker
- Experienced chest pain and palpitations
  - Cardiac work-up was negative
- A CT chest scan identified a few pulmonary nodules and mediastinal lymphadenopathy
- Endobronchial ultrasound (EBUS) FNA of hilar lymph node positive for metastatic adenocarcinoma, most likely of thyroid origin
- Underwent neck ultrasound
  - Multinodular, diffusely heterogenous thyroid gland
  - Left thyroid gland is highly vascular, heterogenous and multinodular with nodular borders difficult to discern

Medical History

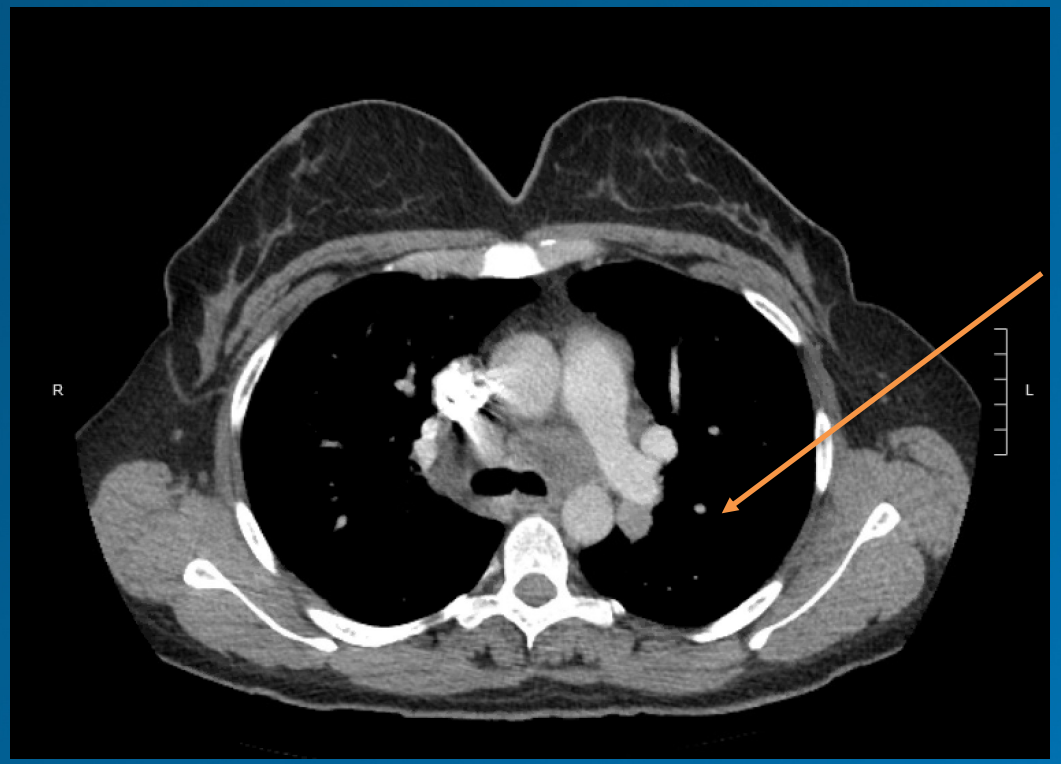
- No significant medical history
- Lived close to Chernobyl as a child at the time of the nuclear disaster
- No regular medications, just NSAIDs

FNA, fine needle aspiration.

AXIS Medical Education

Case: Key Imaging Findings

Chest CT



Thyroid Ultrasound

- There is a multinodular, diffusely heterogenous thyroid gland seen on both sides
- There is an irregular heterogenous, highly vascular area with varying echotexture in the medial mid-pole of the left thyroid lobe, measuring 1.5 x 1.38 x 1.67 cm
- A mid anechoic structure is seen in the left thyroid lobe, measuring 0.44 x 0.42 x 0.18 cm

CT, computed tomography.

AXIS Medical Education

Case: Tissue Diagnosis/Current Status

- FNA of the thyroid is positive for papillary thyroid carcinoma
- Clinical stage T1b N1b M1
- Patient is referred to an endocrine surgeon and an endocrinologist
- Thyroglobulin 7.4 ug/L
- Anti-thyroglobulin Ab 378 IU/mL

FNA, fine needle aspiration.

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Case: Next Step?

- What do you recommend next for treatment?
  a) Radioactive iodine ablation
  b) Total thyroidectomy and central neck dissection
  c) PET scan and brain MRI
  d) Initiate neoadjuvant therapy in anticipation of subsequent surgery
  e) Unsure

MRI, magnetic resonance imaging; PET, positron emission tomography.

AXIS Medical Education

Case: Next Step?

- What do you recommend next for treatment?
  a) Radioactive iodine ablation
  b) Total thyroidectomy and central neck dissection
  c) PET scan and brain MRI
  d) Initiate neoadjuvant therapy in anticipation of subsequent surgery
  e) Unsure

MRI, magnetic resonance imaging; PET, positron emission tomography.

AXIS Medical Education

Case: Total Thyroidectomy Completed

Pathologic Findings

- Papillary thyroid carcinoma, classical (usual, conventional)
- Tumor involves right and left lobes
- Tumor measures 2.7 cm
- Microscopic invasion into extrathyroidal soft tissue
- Chronic lymphocytic thyroiditis

AJCC Staging (8th edition)

- pT3 cN1b M1
- The patient is staged as stage II
  - Patients younger than age 55 are either stage I (M0) or stage II (M1), so this patients has stage II disease

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Case: Plans for Systemic Therapy?

- What would you recommend for systemic therapy?
  a) Start lenvatinib
  b) Start sorafenib
  c) Radioactive iodine ablation
  d) Send tissue for PD-L1 testing
  e) Unsure

PD-L1, programmed cell death protein ligand 1.

AXIS Medical Education

Case: Plans for Systemic Therapy?

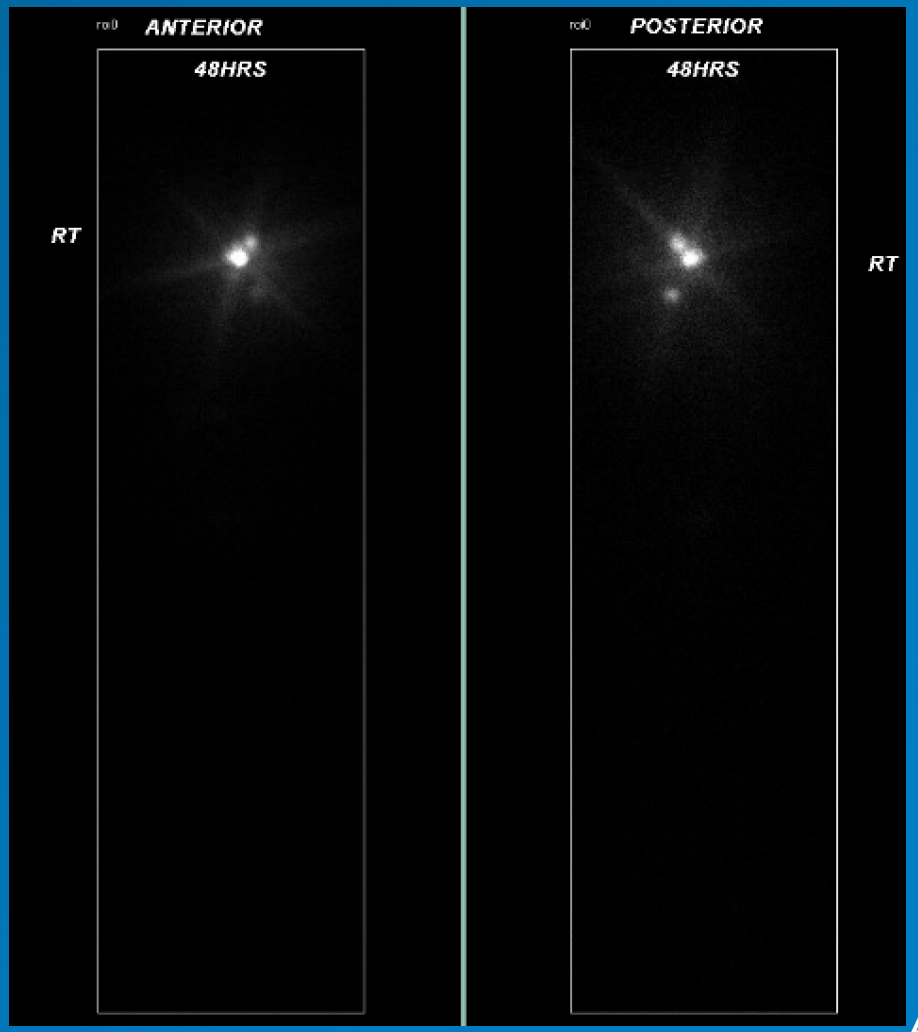
- What would you recommend for systemic therapy?
  a) Start lenvatinib
  b) Start sorafenib
  c) Radioactive iodine ablation
  d) Send tissue for PD-L1 testing
  e) Unsure

PD-L1, programmed cell death protein ligand 1.

AXIS Medical Education

Case: Radioactive Iodine Ablation

- I-131 radioactive iodine ablation performed (375 mCi)
- Post-therapy scan showed multiple areas of uptake in left cervical lymph nodes and mediastinal lymph nodes



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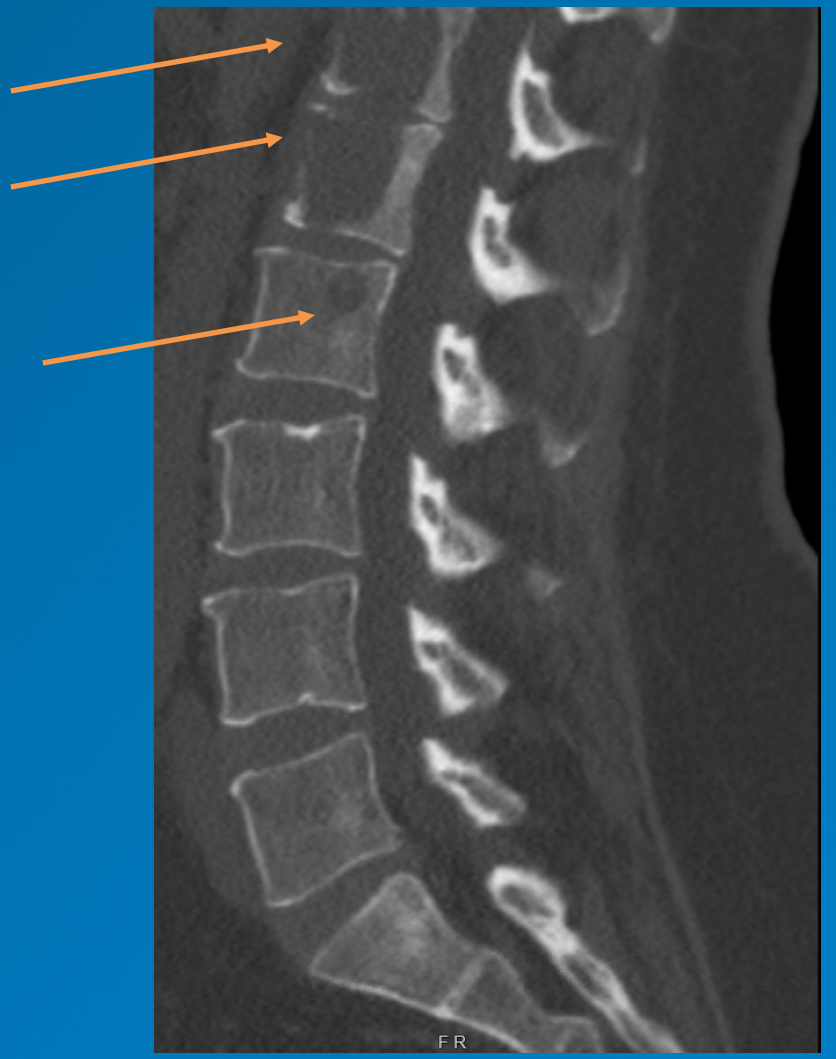
Case: Progression

- 2 months later, the patient complained of new lower back pain
- A CT scan of the chest/abdomen/pelvis identified a new lytic bone lesion in sacrum and iliac bones as well as multi-level vertebral body lytic lesions



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Case: Plans for Systemic Therapy?

- What do you recommend for systemic therapy?
  a) Start lenvatinib or sorafenib
  b) Start immunotherapy with pembrolizumab
  c) Initiate chemotherapy with doxorubicin
  d) Send tissue for NGS testing
  e) Unsure

NGS, next-generation sequencing.

AXIS Medical Education

Case: Plans for Systemic Therapy?

- What do you recommend for systemic therapy?
  a) Start lenvatinib or sorafenib
  b) Start immunotherapy with pembrolizumab
  c) Initiate chemotherapy with doxorubicin
  d) Send tissue for NGS testing
  e) Unsure

NGS, next-generation sequencing.

AXIS Medical Education

Case: Molecular Marker Testing

Comprehensive genomic profiling with NGS

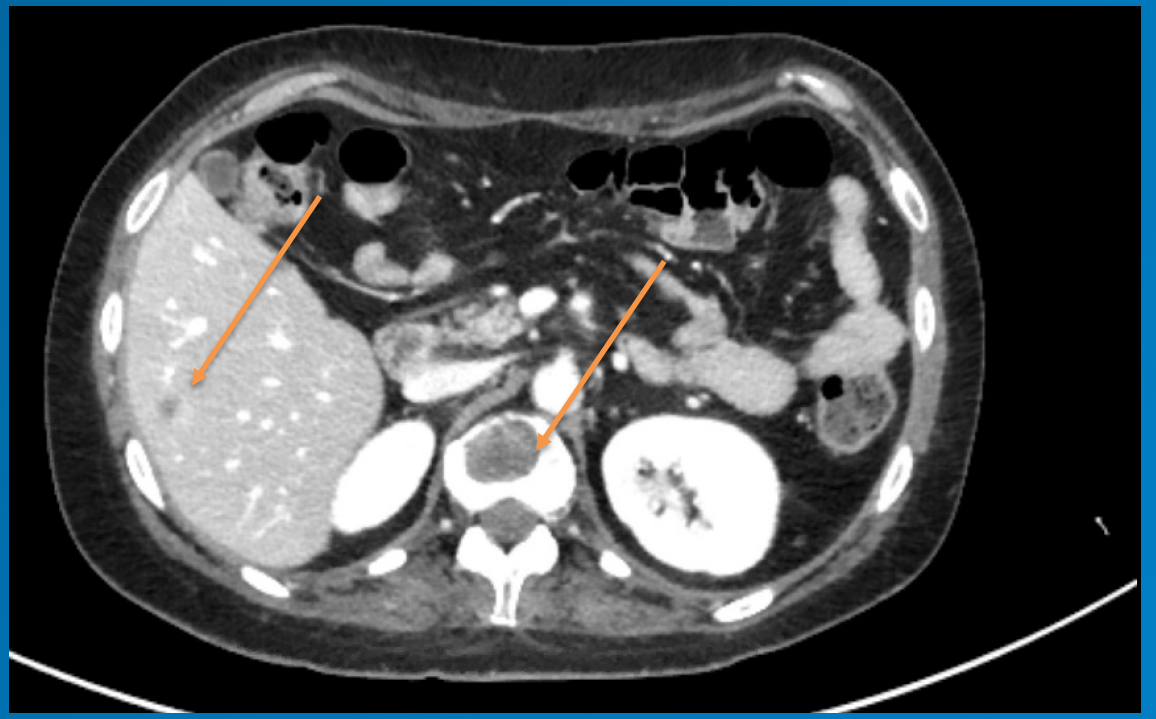
Formalin-Fixed Paraffin-Embedded Tissue Thyroidectomy specimen, Comprehensive Genomic Analysis
Genomic Alterations Detected
FGFR2 A315T, *RET NCOA4-RET* fusion (N7;R12), *RET-NAALADL2* fusion (R11;N13), *TERT* promoter -124C>T
Microsatellite Status (MSI)
MS-Stable
PD-L1 22C3 FDA (Pembrolizumab) Status
High Expression, Tumor Proportion Score: 95%
Tumor Mutational Burden
0 Muts/Mb

PD-L1, programmed cell death protein ligand 1.

AXIS Medical Education

Case: Progression

- Patient started palliative lenvatinib immediately, which she tolerated after 1 dose reduction
- A re-staging scan reported progression of multiple lytic bone lesions and new liver metastases



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Case: Plans for Systemic Therapy?

- What do you recommend now for systemic therapy?
  a) Switch to sorafenib
  b) Switch to immunotherapy with pembrolizumab
  c) Switch to selpercatinib or pralsetinib
  d) Switch to chemotherapy
  e) Unsure

AXIS Medical Education

Case: Plans for Systemic Therapy?

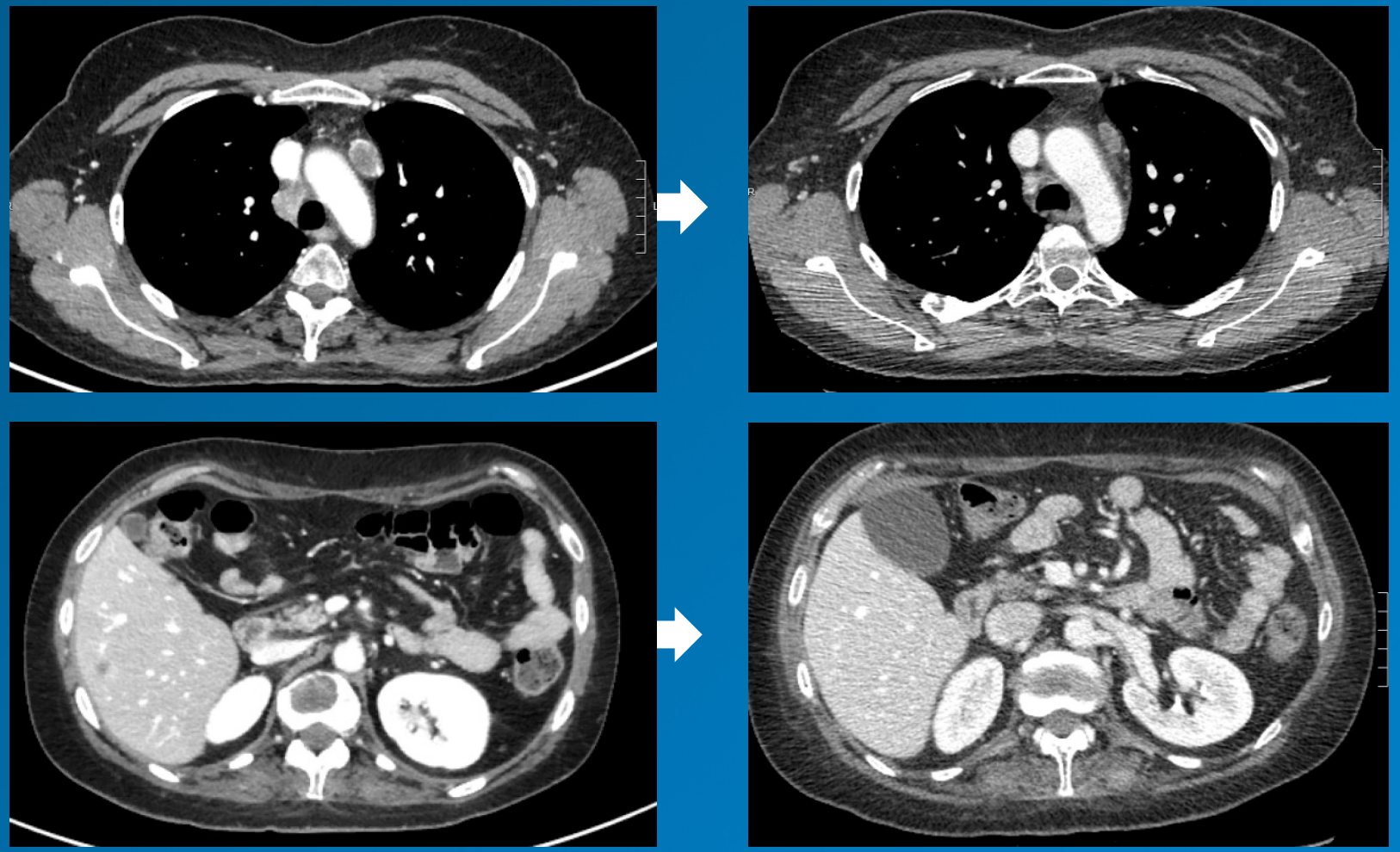
- What do you recommend now for systemic therapy?
  a) Switch to sorafenib
  b) Switch to immunotherapy with pembrolizumab
  c) Switch to selpercatinib or pralsetinib
  d) Switch to chemotherapy
  e) Unsure

AXIS Medical Education

Case: Pre- and Post- Selpercatinib (2 Months)

- She experiences significant improvement in back pain
- CT scan shows very good partial response with more sclerotic bone lesions

Pre- Selpercatinib | **Post- Selpercatinib**



CT, computed tomography.

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Case: Discussion

Discussion Topics

- Treatment selection and rationale
- Recommendations for long-term oral therapy compliance
- Adverse events and management

	Selpercatinib	Pralsetinib
Administration, dose	Oral, 160 mg twice daily	Oral, 400 mg once daily
ORR		
TKI-naïve MTC	73% (n=88)	66% (n=29)
TKI pre-treated MTC	69% (n=55)	60% (n=55)
Systemic therapy-naïve RET fusion-positive TC	100% (n=8)	-
Previously treated *RET* fusion-positive TC	79% (n=19)	89% (n=9)
Adverse events		
Any Grade 3-5 Treatment-related AE	30%	53%

ORR, objective response rate; TKI, tyrosine kinase inhibitor (cabozantinib/vandetanib); MTC, medullary thyroid cancer; TC, thyroid cancer; AE, adverse event.

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Key Takeaways

- Germline *RET* mutation testing should be performed for all patients with newly-diagnosed MTC
- Somatic NGS testing including *RET* should be considered for all patients with MTC with wild-type germline *RET* and all patients with RAI refractory DTC or poorly-differentiated/anaplastic TC
- Selpercatinib and pralsetinib are highly selective RET inhibitors with favorable safety profiles, and are FDA approved options for *RET* mutation–positive MTC or *RET* fusion–positive thyroid cancers
- Solvent-front mutations can confer resistance to selpercatinib or pralsetinib, but second-generation RET inhibitors are being developed to overcome this resistance

DTC, differentiated thyroid cancer; FDA, US Food & Drug Administration; MTC, medullary thyroid cancer; NGS, next-generation sequencing; RAI, radioactive iodine; TC, thyroid cancer.

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A New Chapter for Oral Precision Therapies in Thyroid Cancer:

RET Inhibitors